REMARKS

Claims 1-116 were previously cancelled. Claims 126, 133, 138, 139, 142, 143, and 149-178 were previously withdrawn. Applicants reserve the right to file divisional applications directed to the withdrawn subject matter. Claim 117 has been amended to further define the current invention. Claim 148 has been amended to correct minor typographical errors. Support for the amendments may be found throughout the specification, specifically at page 16, line 31; page 19, lines 17-24; Table 1D; and Examples 13 and 14. No new matter has been added. Claims 117-125, 127-132, 134-137, 140, 141, 144-148, 179, and 180 are currently pending.

Claim Objection

Claim 148 is objected to for minor informalities. Claim 148 has been amended to correct these informalities. Withdrawal of the objection is respectfully requested.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 117-125, 127-132, 134-137, 140, 141, 144-148, 179, and 180 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the phrase "wherein said displacer changes at least one nucleotide or a nucleotide sequence in said recipient polynucleotide duplex when the displacer is introduced into the recipient polynucleotide duplex" adds new matter to the claims. The Examiner states that the claim could be read to read that the displacer changes at least one nucleotide in the recipient polynucleotide duplex of a triplex displacer-recipient complex. See Office Action page 3. In response to Applicants previously submitted remarks the Examiner states that that page 16, line 30 and page 19 lines 17-24 do not describe the claim limitations of claim 117. See Office Action page 5.

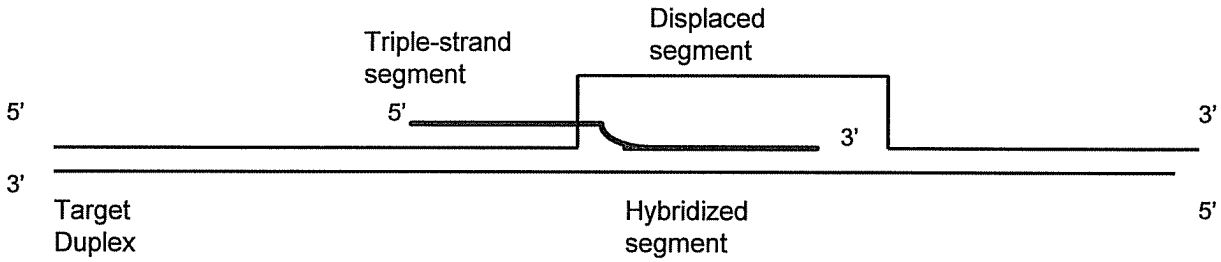
Applicants respectfully traverse the rejection and maintain that the claims satisfy the written description requirement. However, solely in an attempt to promote prosecution, claim 117 has been amended to recite:

> A nucleic acid displacer composition comprising an isolated oligo- or polynucleotide displacer, which binds to or complexes with a recipient

> polynucleotide duplex to form a displacer-recipient complex, said oligo- or polynucleotide displacer comprising two or more sequences:
> a) at least one first sequence which binds or complexes with said recipient polynucleotide duplex through triplex strand formation;
> b) at least one second sequence, said second sequence:
> (i) being complementary to at least a portion of one strand of said recipient polynucleotide duplex and being base-paired with said portion;
> (ii) comprising one or more modified nucleotides that increase stability; and
> (iv) comprising one or more nucleotides that form a mismatch with said strand of the recipient polynucleotide duplex.
> wherein said displacer changes at least one nucleotide or a nucleotide sequence in said recipient polynucleotide duplex of a triplex displacer complex formed by said displacer and said recipient polynucleotide complex when the displacer is introduced to the recipient polynucleotide duplex and said complex is within a cell.

Support for the amendments may be found throughout the specification. For example, page 16, line 31 of the specification reads "In another embodiment, our single stranded displacers are not hybridized to a linker strand and are capable of initiating triple strand formation..." The specification also includes examples illustrating triple strand formation accompanied by strand displacement.

Claim 117 has also been amended to include the triple-strand formation feature in the recitation of the description of the first sequence. The complex that would be formed as part of the composition of claim 117 would be as follows:



where the displacer composition is depicted as the heavy black line. Thus, the first sequence of the displacer participates in triple strand formation [Claim 117 (a)], and is in a parallel (5'-3')

orientation with regard to the top (5'-3') strand; the second sequence of the displacer is complementary to a portion of the recipient target duplex and is hybridized to one strand (and as such is anti-parallel with regard to the bottom (3'-5') strand). Table 1 D of the specification illustrates this type of displacer primer where: (1) the $(TC)_n$ segment of BT-D-MedC (1)-1 will bind to the bottom strand of pMS19 through triple strand formation; and (2) the 3' sequences will are able to hybridize with the top strand of pMS19. The BT-D-MedC Displacer was utilized in Examples 13 and 14. Claim 117 has been further amended to recite that the complex is within a cell.

The complex as recited in newly amended claim 117 allows for hybridization to take place. A mutation occurs within a cell when one or more mismatches are created between the Displacer and the hybridized target strand. The specification teaches:

> One of the significant uses of our invention is for the site specific addition or deletion of nucleotides in a recipient polynucleotide sequence. This process occurs when the new strand is introduced to the recipient duplex and displaces the original strand. The cellular machinery involved in generalized recombination and gene conversion will act to transfer sequence from the displacer strand to the recipient polynucleotide.

See specification page 19, lines 17-24. Applicants respectfully note that the first and second segments may be oriented in either direction--i.e., upstream or downstream (5'-triple –duplex-3') or vice versa (5'-duplex-triplex-3') as these compounds participate in binding reactions and not extensions that would require a particular orientation of a 3' end. The recitation of a displacer strand with triple strand segment is clearly described in the specification and as such claim 117 does not contain new matter.

The present specification contains a clear description of a displacer strand with triple strand segment as recited by the currently amended claims. Claims 117-125, 127-132, 134-137, 140, 141, 144-148, 179, and 180 therefore satisfy the written description requirement. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §102(e)

Claims 117-119, 121, 125, 134-136, 144, 145, 179, and 180 are rejected under 35 U.S.C. §102(e) as being anticipated by Lin *et al.* (U.S. Patent No. 5,214, 136; hereinafter "Lin"). The Examiner cites three main reasons: (1) "the nucleic acid displacer taught by Lin *et al.* has the ability to changes at least one nucleotide or a nucleotide sequence in the recipient polynucleotide duplex which is available in nature when the displacer is introduced into the recipient polynucleotide duplex"; (2) "when the displacer is introduced into the recipient polynucleotide, the recipient polynucleotide recited in claim 117 is not part of a nucleic acid displacer composition"; and (3) "the phrase 'wherein said displacer changes at least one nucleotide or a nucleotide sequence in said recipient polynucleotide when the displacer is introduced into the recipient polynucleotide nucleotide' recited in claim 117 is not a structural limitation of the claim, but is a functional limitation of the claim." See Office Action page 6-8. In response to Applicants' previously submitted arguments, the Examiner contends that the displacer taught by Lin has the ability to change at least one nucleotide of a nucleotide sequence in the recipient polynucleotide duplex and that the recipient polynucleotide duplex and the displacer-recipient complex recited in claim 117 are not parts of the nucleic acid displacer composition. See Office Action page 9.

Applicants respectfully traverse the rejection. Lin describes a displacer which binds or complexes with a duplex. The strand that is purported to be a displacer (which will be referred to as "LD" for Lin's Displacer) is a polyprimidine which is used in a stability assay. The LD hybridizes to its complementary strand ("LC" for Lin's Complement). Although this complementary sequence (LC) is not specified, its sequence may be ascertained from the sequence of LD. Applicants explained in the previously submitted response that Lin does not describe triple strand formation, but rather only refers to normal hybridization of a sequence to its complement. Because the Examiner appears to interpret the present claims in terms the intrinsic properties of Lin, Applicants discuss these properties in light of the present claims.

To function as the displacer of the instant claims, the LD must have the ability to from a complex with a duplex. This can take place through triple strand formation (as recited in the presently amended claims). However, this would not occur through the CCC-CT segment but

rather through the homopolymeric prymidine segment TTTTTTT. Triple strand formation takes place through *parallel binding*, as opposed to *normal Watson-Crick base pairing* which occurs through an anti-parallel orientation. This action would result in two LD strands. The first strand, (which takes part in forming the duplex) will be referred to as LD1, while the strand that binds to the duplex will be referred to as LD2. The normal duplex is depicted below:

```
5′  P-CCC-TCT-TTT-TTT-CCP 3′          LD
3′    GGG-AGA-AAA-AAA-GG  5′          LC
```

The potential triple strand complex formed by a second copy of LP binding to a duplex through the use of the CCC-TCC as suggested by the Examiner will have the following structure.

```
                  5′  P-CCC-TCT-TTT-TTT-CCP 3′        LD1
                  3′    GGG-AGA-AAA-AAA-GG  5′        LC
                      CCC-P 5′                        LD2
3′  PCC-TTT-TTT-TCT
```

Only the terminal 5' end of the suggested CCC-TCT of LP will (potentially) be involved in triple strand formation. There are no bases to pair with other segment (TCT) when aligned in parallel with the LC strand. Formation of this structure may fulfill the first requirement, but it does not fulfill the second requirement as suggested by the Examiner. It is extremely unlikely that the suggested TT-TTT segment will have the ability to bend sufficiently to hybridize with its complementary segment in the LC strand. As such, the TT-TTT may be complementary but it will not be base paired. There is also no evidence that such a twisted binding event would be energetically favorable enough to displace the TT-TTT segment of LP1 from its complementary sequence on LC in the LP1/LC duplex.

Alternatively, triple-stranded binding may take place through the homopolymeric prymidine segment TTTTTTT of LD2. The structure that could potentially form may be

represented by the following:

```
5′  P-CCC-TCT-TTT-TTT-CCP 3′          LD1
3′    GGG-AGA-AAA-AAA-GG  5′        LC
          T-TTT-TTT
    3′ PCC           CT-CCC-P 5′     LD2
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Again, there is no segment in LD2 that would be capable of hybridizing to the LC strand. Thus, despite the fact that the first segment of the Lin oligonucleotides may be matched, the second sequence as defined in the pending claims is completely absent in the Lin sequences. For a rejection under 35 U.S.C. §102 to be properly made and sustained, the art cited in that rejection must disclose each and every element of the claim(s) called out in the rejection. MPEP §2131. Lin does not describe triple strand formation as currently claimed. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §103(a)

Lin *et al.* in view of Dattagupta *et al.*

Claims 146 and 147 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lin as applied above and further in view of Dattagupta *et al.* (U.S. Patent No. 4,737,454; hereinafter "Dattagupta"). The Examiner contends that there is motivation to combine the references because the simple replacement of a type of label on the displacer molecule would have been obvious because the labels are used for the same purpose. (See Office Action pages 10-11). The Examiner also states that the displacer taught by Lin has the ability to change at least one nucleotide in the recipient polynucleotide complex upon introduction of the displacer. The Examiner then concludes that Lin does teach that the displacer changes at least one nucleotide in the duplex. See Office Action pages 10-12. In response to Applicants' previously submitted comments, the Examiner contends that the displacer taught by Lin has the ability to change at least one nucleotide of a nucleotide sequence in the recipient polynucleotide duplex and that the recipient polynucleotide duplex and the displacer-recipient complex recited in claim 117 are not

parts of the nucleic acid displacer composition. See Office Action pages 12-13.

Applicants respectfully traverse the rejection. As explained in detail above, Lin does not describe triple strand formation as currently claimed. Dattagupta does not cure the deficiencies of Lin. Like Lin, Dattagupta teaches only single stranded recipient molecules. The combination of Lin and Dattagupta do not result in the presently claimed invention of a nucleic acid displacer composition which binds with a recipient polynucleotide duplex through triplex strand formation. The references do not render the claims obvious because a person of ordinary skill in the art would have no motivation to combine the references, nor an expectation of success in the combination, because neither reference teaches triplex strand formation. Claims 146 and 147 are not obvious over the combination of Lin and Dattagupta. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Lin *et al.*

Claim 148 is rejected under 35 U.S.C. §103(a) as being unpatentable over Lin as applied above. The Examiner states that there is motivation to alter the Lin displacer to form an artificially constructed polynucleotide comprising a naturally occurring recipient polynucleotide duplex hybridized to the nucleic acid displacer composition because Lin tested the oligonucleotide coupled to anthraquinone *in vitro* and *in vivo* and hybridized the molecule to a single stranded RNA molecule. (See Office Action pages 13-14). The Examiner then contends that Lin does teach changes in at least one nucleotide or nucleotide sequence in the recipient polynucleotide sequence. See Office Action page 14. In response to Applicants' previously submitted arguments, the Examiner contends that the displacer taught by Lin has the ability to change at least one nucleotide of a nucleotide sequence in the recipient polynucleotide duplex and that the recipient polynucleotide duplex and the displacer-recipient complex recited in claim 117 are not parts of the nucleic acid displacer composition. See Office Action pages 15-16.

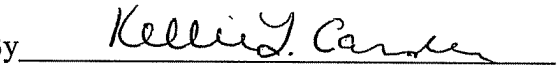
Applicants respectfully traverse the rejection. Lin does not teach a nucleic acid displacer composition which binds with a recipient polynucleotide duplex through triplex strand formation, a structural component required by claim 117 (from which claim 148 ultimately depends). A person of ordinary skill in the art would have no motivation to alter the teaching of

Lin because, as explained above, it is extremely unlikely that the suggested TT-TTT segment will have the ability to bend sufficiently to hybridize with its complementary segment in the LC strand. Such an event would be so energetically unfavorable that there would be no reasonable expectation of success. Claim 148 is not obvious over Lin. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Conclusion

Applicants respectfully submit that all claims are in condition for allowance. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicants would appreciate the courtesy of a telephone call to their counsel at the number listed below to resolve such issues and place all claims in condition for allowance.

Respectfully submitted,
THE WEBB LAW FIRM

By 

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